

Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 119-124 are pending in this application and are rejected on various grounds. Claim 124 has been canceled without prejudice or disclaimer. Claim 119 has been amended for clarity. The rejections to the presently pending claims are respectfully traversed.

Specification

The disclosure was objected to by the Examiner as containing "embedded hyperlink and/or other form of browser-executable code." The foregoing amendment to the specification which deleted all embedded hyperlinks, is believed to overcome the present objections.

In addition, amendments to the specification have incorporated the requisite assurances that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the pertinent U.S. patent."

Accordingly, Applicants believe that all objections to the specification has been overcome.

Continuity

The Examiner asserts that Applicants have not complied with conditions to receive benefit of an earlier filing date under 35 U.S.C. 119(e) because allegedly, the provisional applications listed in the first paragraph of the instant application do not refer to SEQ ID NO: 349 or PRO1097 or ATCC No. 203044. Applicants respectfully traverse.

Applicants submit that they rely on the gene amplification assay for patentable utility of the PRO1097 molecule, its antibodies and nucleic acids encoding it, which was first disclosed in U.S. Provisional Application 60/141037, filed June 23, 1999, priority to which has been claimed in this application. Applicants note that the sequences disclosed in the U.S. Provisional Application No. 60/141,037 have a different sequence listing and a different Figure numbering from that of the current application; therefore, the sequence of PRO1097 is listed as SEQ ID NO: 41 and 42, and Figure 29 and 30 in U.S. Provisional Application 60/141,037. Hence, Applicants are entitled to the benefit of the above provisional application and accordingly, to an effective filing date of at least **June 23, 1999**. The Examiner is respectfully requested to reconsider this application's priority based on this clarification.

Claim Rejections – 35 USC § 101 and 112, first paragraph

Claims 119-124 are rejected under 35 U.S.C. §101 allegedly “because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.” Claims 119-124 are further rejected under 35 U.S.C. §112, first paragraph allegedly “since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention”.

The Examiner asserts that "no well established utility exists for newly isolated complex biological molecules". Regarding the gene amplification data, the Examiner asserts that "a slight increase in clone numbers in a cancerous tissue is no doubt due to an increased number of chromosomes, a very common characteristic of cancerous and non-cancerous epithelial cells" and quotes articles like Hittelman *et al.* and Crowell *et al.* to show that the asserted utility is not specific. The Examiner quotes exemplary articles like Pennica *et al.* and Haynes *et al.* to show that "it does not necessarily follow that an increase in gene copy number results in increased gene expression and increase protein expression, such that the antibodies would be useful diagnostically or as a target for cancer drug development". The Examiner further asserts that no utility for PRO1097 exists even if the specification implies a credible, specific and substantial utility for PRO1097 based on structural identity and quotes exemplary articles like Skolnick *et al.*, Bork *et al.*, Doerks *et al.*, Hesselgesser *et al.* and Blease *et al.*, to show that "function cannot be predicted based solely on structural similarity to a protein found in sequence databases." For the reasons outlined below, Applicants respectfully disagree.

Utility Guidelines

According to the Utility Examination Guidelines (“Utility Guidelines”), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted “specific, substantial, and credible utility” or a “well-established utility.”

Under the Utility Guidelines, a utility is “specific” when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of “substantial utility” defines a “real world” use, and derives from the Supreme Court’s holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that “The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility.” In explaining the “substantial utility” standard, M.P.E.P. 2107.01 cautions, however, that **Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement.** “Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a “substantial” utility.” (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P. 2107 II (B) (1) gives the following instruction to patent examiners: “If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.”

Finally, the Utility Guidelines restate the Patent Office’s long established position that any asserted utility has to be “credible.” “Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the Applicant’s assertions.” (M.P.E.P. 2107 II (B) (1) (ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

To overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.** Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the

burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Arguments

Initially, Applicants submit that an assertion for utility of PRO1097 is not based on structural similarity. Thus, the articles cited by the Examiner that discuss utility based on structural similarity, namely, Skolnick *et al.*, Bork *et al.*, Doerks *et al.*, and Hesselgesser *et al.*, have no bearing on the issue of utility. In the present case, Applicants have shown experimentally that the DNA encoding PRO1097 is amplified in human lung adenocarcinomas or squamous cell carcinomas and Applicants rely on this gene amplification data for patentable utility of this case. Thus the claimed utility for the PRO1097 antibodies is based on its use in the diagnosis of lung or colon cancer, as explained below.

A prima facie case of lack of utility has not been established

The Examiner bases her conclusion, that increases in gene copy number does not reliably correlate with increased gene expression or polypeptide expression, on exemplary literature reports like Pennica *et al.*, and Haynes *et al.*, and hence concludes that PRO1097 polypeptides and their antibodies lack utility.

According to the Examiner, Pennica *et al.* teaches that "An analysis of *WISP*-1 gene amplification and expression in human colon tumors **showed a correlation between DNA amplification and over-expression**, In contrast, *WISP*-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient." (Emphasis added). Firstly, Applicants draw attention to Pennica's showing that "a correlation between DNA amplification and over-expression exists for the *WISP*-1 gene" in 84% of the tumors examined. While Pennica discloses a lack of correlation for the *WISP*-2 gene, Pennica teaches nothing regarding such a lack of correlation in genes in general. That is, Pennica's teachings are specific for the *WISP* family of genes, and are not directed to genes in general. The Utility Guidelines requires that for a *prima facie* showing of lack of utility, the Examiner has to provides evidence that it is **more likely than not** that a lack of correlation between protein expression and gene amplification

exists, in general. Accordingly, Applicants respectfully submit that Pennica teaches nothing of the correlation between gene amplification and polypeptide over-expression in general.

The Examiner adds that "Haynes *et al.* studied 80 proteins... and found no strong correlation between proteins and transcript levels." Applicants respectfully traverse and point out that, on the contrary, Haynes teaches that "**there was a general trend** but no strong correlation between protein [expression] and transcript levels" (Emphasis added). Haynes studied 80 *yeast* proteins to show that "protein levels cannot be **accurately** predicted from the level of the corresponding mRNA transcript" (Emphasis added) (see page 1863, paragraph 2.1, last line). For example, in Figure 1, there is a positive correlation between mRNA and protein amongst **most** of the 80 yeast proteins studied but the correlation is "not linear" and hence, "one cannot **accurately** predict protein levels from mRNA levels." In fact, very few data points deviated or scattered away from the expected normal or showed a lack of correlation between mRNA: protein levels. In fact, the Haynes data, meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Thus, Applicants submit that the Examiner's rejection is based on a misunderstanding of the scientific data presented in Haynes *et al.*

In conclusion, the Examiner has not shown a lack of correlation between gene amplification and polypeptide over-expression, in general. Since the standard is not absolute certainty, based on Pennica alone, a *prima facie* showing of lack of utility has not been made in this instance.

It is "more likely than not" for amplified genes to have increased mRNA and protein levels

Applicants submit further exemplary articles to show that, the art indicates that, generally, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. For example, Orntoft *et al.* (Mol. and Cell. Proteomics, 2002, Vol.1, pages 37-45) studied transcript levels of 5600 genes in malignant bladder cancers many of which were linked to the gain or loss of chromosomal material using an array-based method. Orntoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* (Cancer Res., 2002,

Vol. 62, pages 6240-45) showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene expression levels." (see page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.*, (PNAS, 2002, Vol. 99, pages 12963-12968) who studied a series of primary human breast tumors and showed that "...62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

Also enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these

experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, although there are some examples in the art of genes that do not fit within the central dogma of molecular biology, these instances are exceptions rather than the rule. In the vast majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1097 gene, that the PRO1097 protein is concomitantly overexpressed. Thus, Applicants submit that the PRO1097 proteins and nucleic acids have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the protein for diagnosis of cancer.

Claimed proteins would have diagnostic utility even if the protein were not overexpressed

Even assuming *arguendo* that, there is no correlation between gene amplification and increased mRNA/protein expression for PRO1097, which Applicants submit is not true, a polypeptide encoded by a gene that is amplified in cancer would **still** have a credible, specific and substantial utility. In support, Applicants submit a Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the instant application. Dr. Avi Ashkenazi's Declaration explains that:

even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene

product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician need not treat a patient with agents that target that gene product. This not only saves money, but further prevents unnecessary exposure of the patient to the side effects of gene product targeted agents.

This is further supported by the teachings of the attached article by Hanna and Mornin. The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

In conclusion, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO1097 polypeptide based on the gene amplification results for the nucleic acid, for example, in detecting over-expression or absence of expression of PRO1097. In fact, the art also indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will also be expressed at an elevated level. Further, based on the instant disclosure, the functional recitation in the claims, one skilled in the art, at the time the application was filed, would know how to make and use the claimed polypeptides, without undue experimentation.

Thus, Applicants have demonstrated utility for the PRO1097 polypeptide as a tumor marker for lung and colon cancer and antibodies thereof are useful in their diagnosis. Accordingly, the present rejections under 35 U.S.C. §101 and §112, first paragraph should be withdrawn.

Claim Rejections – 35 USC § 112, first paragraph- Deposit Rules

Claims 119-124 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner required that "elements required for practicing a claimed invention must be known and readily available to the public or obtainable by a repeatable method set forth in the specification."

Applicants submit that amendments to the specification have (1) the current ATCC address; and (2) incorporated the requisite assurances that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the pertinent U.S. patent." Additionally, the specification recites the correct ATCC address. Thus, Applicant have fulfilled the requirements of 37 C.F.R. § 1.809(d) and therefore, this rejection should be withdrawn.

Claim Rejections – 35 USC § 112, second paragraph

Claims 119 and 124 are rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. The Examiner states that the claims are rendered indefinite for reciting "binds" and "specifically binds".

Without acquiescing to the propriety of this rejection and solely in the interest of expedited prosecution in this case, Applicants have canceled claims 124 and have amended claim 119 to recite "specifically binds". Applicants submit that the art-recognized meaning of "specific" binding is that the antibody that specifically binds to a particular antigen, and does not significantly cross-react with another antigen. Contrary to what the Examiner says, one skilled in the art would know what the scope of the invention is.

Accordingly, Applicants submit that the claims are definite and respectfully request that this rejection be withdrawn.

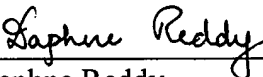
The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C30).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: September 10, 2004



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